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EXAMINER				
BORIN, MICHAEL L				
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

# Office Action Summary

**Application No.**

10/782,061

**Applicant(s)**

ZEMLA, ADAM T.

**Examiner**

Michael Borin

**Art Unit**

1631

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 03 April 2009.  
2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.  
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 14 and 19-25 is/are pending in the application.  
4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.  
5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.  
6) ☒ Claim(s) 14 and 19-25 is/are rejected.  
7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.  
8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.  
10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)  
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)  
3) ☐ Information Disclosure Statement(s) (PTO-8508)  
Paper No(s)/Mail Date \_\_\_\_\_  
4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_  
5) ☐ Notice of Informal Patent Application  
6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

1. A request for continued examination under 37 CFR 1.114 filed on 12/11/2008 is noted. As addressed in the NOTICE OF IMPROPER REQUEST FOR CONTINUED EXAMINATION of 12/22/2008, continued examination under 37 CFR 1.114 does not apply to an application unless prosecution in the application is closed. As the RCE was accompanied by a reply to a non-final Office action, the reply was entered and is now considered under 37 CFR 1.111

### **Status of Claims**

2. Claims 15-18 are canceled. Claims 19-25 are added. Claims 14,19-25 are pending.

Applicant's arguments have been fully considered and were deemed to be persuasive-in-part. Rejections and objections not reiterated from previous Office actions are hereby withdrawn. The following rejections are either reiterated or newly applied as necessitated by amendments. They constitute the complete set presently being applied to the instant application.

***Claim Rejections - 35 USC § 112, first paragraph (New Matter).***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 14, 19-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The rejection is made for the following reasons:

A. Claim 14 introduces new matter because, as addressed in the preceding office action, the language incorporated from now canceled claim 18 identifying plurality of distance scores, wherein each distance score corresponds to a number of pairs of residues in the correspondence that are within a pre-determined distance of a plurality of pre-defined distances

is not supported by the language in the specification.

Applicant argues that the language "global distance test value", is supported in the instant specification, for example, at paragraph [0041]. However, the rejection addresses not the step of detection of "global distance test value", but the preceding step of identifying distance scores.

B. Further, with regard to the step of "selecting global distance test value" (emphasis added), the term "selecting" represents a new matter, as specification, while disclosing how to determine a GDT value, does not describe how to select it.

C. Further, the amended claim language addressing LCS analysis:

**determining** a plurality of root mean square deviations corresponding to a plurality of sets of pairs of residues ... wherein the plurality of root mean square deviations are **determined** using a plurality of specified threshold values

is viewed as new matter.

Specification does teach "selecting RMSD or distance cutoff" (see paragraph [0072], for example), i.e., it teaches that a threshold RMSD can be selected, but it does not teach that an RMSD is determined (i.e., an extra step of determining is involved) using such a threshold value.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 15-18 are canceled and their limitations are included, in part, into claim 14. Therefore, the rejection under USC 102 is vacated and the following rejection under 35 U.S.C. 103(a) is applied.

4. Claims 14, 19-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zemla et al. (Proteins: Structure, Function, and Genetics vol. 45, Issue S5, Pages 13-21. Published Online: 28 Jan 2002) and Cristobal et al. (BMC Bioinformatics 2001, 2:5. Published 1 August 2001).

Zemla et al. teach global distance test (GDT) software including determination of Longest Continuous Segment (LCS), and extension of the software including the local-global alignment package (LGA).

With respect to identifying a longest contiguous segment comprising a plurality of contiguous positions, in the reference, a comparison of secondary structure assignments in the target and model, and the longest continuous segment (LCS) analysis are carried out. These plots identify precisely the LCS in the model structure that do not deviate from the target by more than a specified  $C\alpha$  RMSD. p. 16, left column.

With respect to identifying a global distance metric based on a number of pairs of residues, in the reference, the global distance test (GDT) summary graphs provide an approximate sorting of predictions by quality and a good starting point for further analysis (Fig. 3). These plots consist of points identifying subsets of structure that can be fitted under a specified distance cutoff. Similarity between predicted and experimental structures may be assessed over regions that are not necessarily continuous in sequence. p. 16, left column. In particular, the GDT\_TS (total scores)

measure provides a reasonable single-value approximation of the tertiary structure prediction quality. Total scores, GDT\_TS provide a single-value approximation of the tertiary structure prediction quality. The GDT\_TS is defined as an average of four separate GDT calculations identifying maximal sets of residues at 1, 2, 4, and 8 Å distance cutoffs. Paragraph bridging pages 16-17.

Further, as sequence-dependent superposition methods are unable to identify regions of structural similarity in a prediction that are not correctly aligned by sequence, sequence-independent LGA algorithm is being used.

Similarly, Cristobal et al. teach LGA program for structure comparative analysis of two selected 3D protein structures. The LGA analysis can be made in two general modes (see last section of the article):

- Alignment dependent analysis. This mode can be used when two protein structures are identical by the numbering of their amino-acid sequences. Under this mode (LCS and GDT analysis) the program is able to identify the segments where two structures are identical, and the segments where they differ.
- Alignment independent analysis. This mode can be used for structural comparison of any two proteins. The best superposition (according to the LGA technique) is calculated completely ignoring the alignment relationship between the two proteins. The suitable amino acid correspondence (structural alignment) is reported.

The LGA algorithm searches for the best structural alignment of two proteins according to the LCS and GDT scores calculated for each analyzed alignment independent superposition.

The measures LCS and GDT established for detection of local and global structural similarities between two proteins were successfully verified during the CASP process providing a very good ranking of the evaluated protein models.

When comparing two protein structures the LCS procedure is able to localize (along the sequence) the Longest Continuous Segments of residues that can fit under the selected RMSD cutoff, while the Global Distance Test (GDT) algorithm is designed to complement evaluations made with LCS searching for the largest (not necessary continuous) set of "equivalent" residues deviating by no more than a specified DISTANCE cutoff. The combined LCS and GDT scores produce the LGA-S number which is used to determine the best structural alignment.

The additional LGA-Q value reported in the output from the LGA program is calculated for the final superposition. This number ranks the quality of the alignment and is obtained from the formula:  $Q = 0.1 \cdot N / (0.1 + \text{RMSD})$ , where N denotes the number of residues superimposed under the specified distance cutoff (by default 5), and RMSD is the root mean square deviation calculated on these residues. For rather "weak" alignments the LGA-Q is less than 2.0.



Cristobal reference teaches that for automatic assessment of protein structure the best approach is to combine sequence-independent and sequence-dependent methods. See section "Conclusion". The limited list of sequence-independent and sequence-dependent methods is provided in Table 1. As one of sequence-dependent methods, the reference describes the Global Distance Test which is an estimation of the largest number of residues that can be found where all distances between the protein structures are shorter than the cutoff distance. The number of residues is measured as a percentage of the length of the target structure. The measure used is GDT TS, which is the average of four measures with D = 1,2,4 and 8 Å. See fifth page of the reference, left column. As a sequence-independent method, the reference such method as LGA which utilizes LCS procedure to localize (along the sequence) the Longest Continuous Segments of residues that can fit under the selected RMSD (see discussion of the reference in the rejection under USC 102(b) above.

In *KSR Int'l v. Teleflex*, the Supreme Court, in rejecting the rigid application of the teaching, suggestion, and motivation test by the Federal Circuit, indicated that

The principles underlying [earlier] cases are instructive when the question is whether a patent claiming the combination of elements of prior art is obvious. When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability.

*KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1740 (2007).

Applying the KSR standard of obviousness to the reference of Cristobal, Examiner concludes that the combination of sequence-independent and sequence-dependent methods is an "obvious to try" choosing from a finite number of identified, predictable

solutions. Cristobal suggests that it will benefit automated assessment of protein structure to combine sequence-independent and sequence-dependent methods. The claimed combination is thus were obvious because it would have been obvious to try the known methods for comparing 3D protein structures, with a reasonable expectation of success.

With respect to newly added claims 19-25, if there are any differences between Applicant's claimed method and that of the prior art, the differences would be appear minor in nature. Although the prior art do not teach the various permutations of generating correspondences, and data presentations, the nature of the problem to be solved – detecting similarity between two protein structures - would lead inventors to look at references relating to possible factors known to affect detecting and then presenting such similarity. One of ordinary skill in the art would have been motivated to combine all known factors with no change in their respective functions, and the combination would have yielded nothing more than predictable result.

#### Response to arguments

As applicant's arguments are based on Declaration of Dr. Zemla, the Declaration is discussed herein.

First, the Declaration, paragraphs 11-14 provides a detailed discussion of publication "LGA, a method for finding 3D similarities in protein structures", Nucleic

Acids Research, 2003, Vol. 31, No. 13 ("Zemla NAR"). Despite applicant's claim that this publication is incorporated by reference, no such incorporation by reference was identified neither in the instant specification, nor in the priority application.

Second, in discussing the Crystobal reference, the main issue addressed in the Declaration is that the reference does not address pluralities of parameters— plurality of rmsd, plurality of distance scores – as required by the instant claims. Examiner respectfully disagrees. With respect to plurality of distance scores (distance score is a value corresponding to number of pairs of residues that are within a pre-defined distance), Crystobal teaches that

The Global Distance Test measure is an estimation of the largest number of residues that can be found where all distances between the model and the correct structure are shorter than the cutoff D.

(compare to definition in the claims : "distance score corresponds to a number of pairs of residues in the correspondence that are within a pre-defined distance")

Crystobal teaches determining the scores for four (i.e., multiple) distances (four measures with  $D = 1, 2, 4$  and  $8 \text{ \AA}$ ). Applicant argues that

"the measure used in this [Crystobal] study was GDT TS, which is the average of four measures with  $D = 1, 2, 4$  and  $8 \text{ \AA}$ . This average value deterministically produces the same value based on averaging a plurality of distance values, not by "selecting a global distance test value based on the plurality of distance scores", as required by the claimed invention.

Examiner disagrees. Crystobal indeed averages four scores. However, first, before that, each score , i.e., a number of pairs of residues in the correspondence that are within a pre-defined distance is determined. Second, averaging, as in Crystobal, reads on the broad claim language "based on" (i.e., language "global distance test value based on the plurality of distance scores"). Third, the same averaging as in Crystobal is used in the

instant method – see specification, paragraph [0082] of PreGrant publication – and there is no other disclosure of calculating global distance test value based on the plurality of distance scores.

With respect to using plurality of rmsd, Christobal addresses publication of Zemla (i.e., inventor of the instant method), reference #20, Zemla et al. Proteins: Struct. Funct. Genet. 1999, Suppl 3:22-29. In this publication, Zemla et al teaches determining LCS for three (i.e., plurality) rmsd – see Fig. 2 caption (“the three blue lines correspond to segments superimposable under 1, 2, and 5 Å ° RMS deviation”) and Fig. 2(c).

### ***Conclusion.***

5. No claims are allowed

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. The examiner can normally be reached on 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael Borin, Ph.D./

Primary Examiner, Art Unit 1631

